Research Resources Reporter

November 1982, Volume VI, No. 11

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Serving Animal Resources,
Biotechnology Resources,
General Clinical Research Centers,
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This Issue:

Peritoneal Drug Delivery
Adult Hyperactivity
SLE and Autoimmunity
Hormone Influences Cancer

by
Greg Freiherr

Medical Expertise Applied to Dental Research

Pathologists examine the behavior of bacteria to determine which ones damage teeth, gums, and the heart. A physicist, a biochemist, and an epidemiologist look for signs of toxicity in the dentist exposed to mercury. Engineers develop sensors to monitor dental health and metabolic disease. Electrical techniques developed by orthopedists to speed the healing of fractures are modified to straighten teeth more efficiently.

"These and other efforts going on at the Dental Clinical Research Center demonstrate the interdependence of dentistry and medicine," says Dr. Irwin Ship, professor of oral medicine at the University of Pennsylvania in Philadelphia.

As director of the university's W. D. Miller Dental Clinical Research Center (DCRC), Dr. Ship and the center's principal investigator, Dr. D. Walter Cohen, promote studies in which expertise and knowledge gained in traditionally medical disciplines are used to

Dental appliance that selectively administers electricity to teeth: *first step toward reducing the time orthodontic braces must be worn?*

DCRC *continued*

improve dental health care. "What physicians know about human physiology and pathology gives us a better understanding of diseases that primarily affect oral tissue," says Dr. Cohen, dean of the University of Pennsylvania School of Dental Medicine.

Physicians agree that poor management of metabolic diseases may lead to serious complications. Fluctuating serum glucose levels in diabetics may cause eye or kidney problems. Diabetes may also cause the inflammation and destruction of tissues that surround and support the teeth, a condition called periodontitis. Dr. Robert Friedman, assistant professor of oral medicine at the University of Pennsylvania, says that diabetics generally have an unusual degree of periodontal disease, suggesting that better management of diabetes could reduce the incidence and severity of oral disease in these patients.

Studies done at the DCRC by Dr. Friedman show that diabetics have abnormally high levels of fluid glucose in the gingival crevice, the space between the teeth and the gums. Recent studies at the DCRC revealed that not only the glucose level in the crevice but also the volume of gingival crevice fluid (GCF) varies according to the serum level of glucose, a finding that may allow physicians to easily gauge the effectiveness of management therapy for diabetes. Currently a blood test is the only means available to physicians for determining serum glucose levels. But with a microcapillary tube made of silicon, Dr. Friedman can record the volume and composition of GCF and painlessly, simply, and accurately calculate the level of GCF glucose.

The next logical step is to monitor GCF glucose automatically. Prototypes of electronic sensors that can be placed unobtrusively in the mouth are already being developed by the DCRC in conjunction with the university's dental bioengineering center and chemical electronics center. Sensors now being designed will specifically monitor pH, calcium, phosphate, fluoride, or glucose. Dr. Jay N. Zemel, director of the chemical electronics center, hopes that a second generation of devices can be built to monitor several chemicals or chemical factors simultaneously. These sensors would be used in a variety of experiments that would not constrain patients to a laboratory environment and would make it possible to examine the interaction of plaque, caries, and food in natural or realistic experiments. "What is known about the formation of caries is based on laboratory data and a lot of theory," says Dr. Samuel L. Yankell, a University of Pennsylvania biochemist responsible for testing and evaluating the sensors. "Almost nothing is known about what actually happens in plaque."

At present Dr. Zemel and his team are attempting to prove the feasibility of oral chemical sensing with the development of sensors for the calcium level and the pH of plaque. The presence of food, particularly sugar, affects the growth of bacteria and the pH of plaque. As the plaque pH becomes more acid, calcium in the tooth begins to dissolve, and calcium ions appear in plaque and saliva. Correlating plaque pH and calcium level with bacterial activity would provide a good measure of the patient's dental health and might eventually be used to improve diagnosis, therapy, and management.

But such correlates will rely on rapid and reliable measurements. Available methods are inadequate. They involve scraping plaque from teeth, placing bulky electrodes on or into plaques with wires running out of the mouth, or the use of existing pH telemetry sensors, which require space from missing teeth and are, therefore, limited mainly to use with elderly patients.

The pH sensor being developed at the DCRC should overcome these problems. It is designed to be built into removable dental appliances or orthodontic brackets. Initially, wires will link the sensor to recording instruments outside the mouth, but these will ultimately be replaced by a miniature, battery-powered telemetry unit that will transmit data to

Photo by Greg Freiherr

Dr. D. Walter Cohen, dean of the University of Pennsylvania School of Dental Medicine and principal investigator of the DCRC: *"What physicians know about human physiology and pathology gives us a better understanding of diseases that primarily affect oral tissue."*

Research Resources Reporter

Published monthly by the Research Resources Information Center

A publication of the Division of Research Resources, National Institutes of Health

Correspondence should be addressed to:
Research Resources Information Center
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Rockville, Maryland 20852
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(Prepared under contract with Tracor Jitco, Inc. NO 1-RR-9-2114)

Photo by Greg Freiherr

Dr. Jay N. Zemel, director of the University of Pennsylvania chemical electronics center: *developing sensors to correlate biochemical activity with oral disease.*

Photo by Dr. John Hayden, University of Pennsylvania Health Affairs

Dr. Irving Shapiro: *assessing the levels of mercury in dentists and their assistants.*

receivers in the laboratory. Clinical testing of the sensors will be done at the DCRC, where collaboration was initiated between dental researchers and engineers in the University of Pennsylvania School of Engineering and Applied Sciences. "Although microsensors are research tools at this time, they will certainly contribute to preventive dentistry by allowing dentists to monitor chemical changes that precede the destruction of gums and teeth," Dr. Zemel says.

Correlation between these indicators and the prevalence of dental disease, particularly cavities, could provide standards for such products as food additives, chewing gum, candy, cookies, and cereals. These and other food products serve as the medium on which oral bacteria feed. Brushing, flossing, and regular professional cleanings are needed to keep bacterial plaque at a manageable level. Checkups are essential. "Even advanced stages of periodontal disease are often painless, and development of the disease is slow," Dr. Ship says, "so that it goes unnoticed by the patient."

Gums first become tender and swollen with occasional bleeding around the teeth, a condition called gingivitis. Next the gums change from pink to an unhealthy red. In advanced stages, the gums recede permanently and bone supporting the teeth is damaged.

"Approximately 90 percent of the adults in the United States have at least mild periodontal disease," says Dr. Max Listgarten, professor of periodontics at the University of Pennsylvania. "Most cannot avail themselves of extensive treatment because of the expense, so prevention of serious cases by quickly identifying the early stages of the disease and applying treatment is extremely important."

Dr. Listgarten, an expert in the cellular pathogenesis of periodontal disease, Dr. Norton Taichman, chairman of the pathology department of the University of Pennsylvania, and their colleagues are now trying to determine if differential bacteria counts are indicators of disease activity. "If they are, we want to use these counts to determine how frequently patients should have their teeth cleaned," Dr. Listgarten says.

The researchers are particularly interested in two types of bacteria—spirochetes and motile rods. Research done at the DCRC documents an association between elevated levels of these two types of bacteria and the presence of periodontitis, the most advanced stage of periodontal disease. At this stage, pockets of the bacteria have severely damaged the tissue and bone that support teeth, causing gums to recede permanently and teeth to loosen. Often these teeth must be extracted.

To prevent the onset of periodontitis, plaque must be scraped from the mouth regularly. Research indicates that teeth cleaning every 2 weeks controls the repopulation of bacteria. Annual cleaning does not. "For most patients, cleanings every 2 weeks are prohibitively expensive and not needed. Arbitrary recalls every 6 months may not be soon enough for some, but they may be too frequent for others," Dr. Listgarten says. "By measuring the repopulation rates of spirochetes and motile rods in each patient, recording the proportions of these microorganisms, and comparing the data to levels associated with tissue damage, it should be possible to establish optimal recall intervals."

Dentists could then concentrate on patients who need the most attention, reducing the costs of dental care for disease-resistant patients and intervening early to reduce or eliminate the cost of therapy for patients who are susceptible to disease.

Dr. Listgarten and his colleagues are now studying the

DCRC *continued*

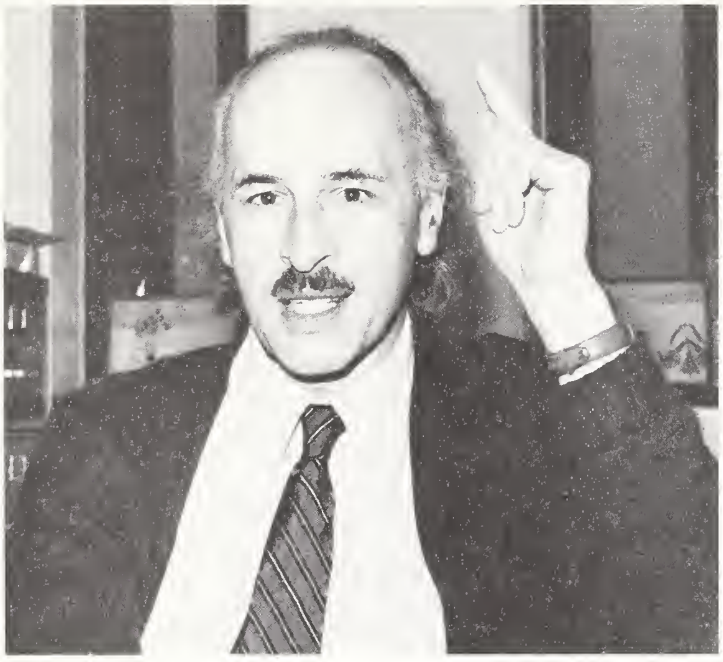

Photo by Greg Freiherr

Dr. Norton Taichman, chairman of the pathology department at the University of Pennsylvania and researcher of juvenile periodontitis: *"I believe we are on the verge of a breakthrough in being better able to diagnose, treat, and perhaps prevent this disease."*

Photo by Greg Freiherr

Technician builds dental appliances for DCRC research: *enhancing dental research with biotechnology.*

repopulation rates of bacteria in some 60 patients. Half of these patients follow individually tailored cleaning schedules. The other half, who serve as the control group, receive cleanings twice yearly, a schedule commonly recommended by practicing dentists.

The researchers are tailoring schedules according to a test that Dr. Listgarten describes as being "remarkably simple." "Just scrape bacteria from the mouth, count the first 200 cells, and come up with a proportion of spirochetes and motile rods in this field," he says. "Any well-trained hygienist can learn to do it."

As a result of this test, some DCRC patients have not had their teeth cleaned since the study began 3 years ago nor have they shown any tooth or gum damage. Others have required cleanings every 2 to 3 months.

Comparing the dental health of the experimental and control groups will determine the benefits of a customized schedule versus the arbitrary 6-month recall program. Results now favor the tailored schedule. If these preliminary findings are confirmed, the study could lead to a preventive regimen that would save time and money as well as improve oral health, Dr. Listgarten says.

But even the most rigorous preventive and therapeutic treatments sometimes cannot stop severe periodontitis from occurring, particularly the type that attacks children and young adults. Dr. Taichman and his associates suspect that immune defects allow the rampant destruction of gum and bone that is characteristic of juvenile periodontitis (JP), a disorder that often leads to the loss of teeth during adolescence. The disease occurs rarely, but when it does, little can be done to stop it. "Juvenile periodontitis causes untold emotional, physical, and economic hardship for patients and their families," Dr. Taichman says.

He theorizes that the response and activity of antibodies and white blood cells in these children is weaker than normal. When the rod-shaped bacterium *Actinobacillus actinomycetemcomitans* (AA) invades the gingival crevice of these patients, it releases a toxin that destroys most or all of the white blood cells in the area. Resultant tissue damage and the proliferation of the bacteria cause serum to leak into the crevice. The serum feeds the bacteria, and toxin production increases.

Antibody response is slow and is neutralized by the toxin, according to Dr. Taichman. White blood cells and monocytes from elsewhere in the body never reach the infected gingival crevice or do so in limited and inconsequential numbers.

Without an effective counterattack, AA and other bacteria proliferate wildly and inflict heavy tissue damage. The disease accelerates, spreads to other sites, and the cycle is repeated. If not controlled, juvenile periodontitis ultimately destroys the bone that supports the teeth. According to reported cases, patients have lost some or all teeth between ages 12 and 30.

Clinical and laboratory studies conducted at the DCRC and elsewhere support Dr. Taichman's theory of the role of AA. Although pockets of the disease harbor a complex mixture of bacteria, AA is present in commanding numbers; antibody levels in the sera and the gingival crevices of patients with JP are high; and AA rapidly induces bone loss in the tooth sockets of laboratory animals. The studies have shown that a strain of the bacterium called Y4, which is present in JP patients, produces two highly active toxins—one that promotes bone resorption and another that destroys white blood cells and monocytes.

"A majority of the children with clinically detectable JP show signs of having been infected with AA," Dr. Taichman says. "The disease is localized

Dental hygienist at the University of Pennsylvania DCRC counts bacteria in a plaque sample: *applying biomedical expertise to research in dentistry.*

to only a few teeth in patients who develop a high titer of antibodies against the Y4 strain of AA, whereas the disease involves many teeth in those who do not develop a good immune response."

Dr. Taichman and his colleagues at the DCRC hope to characterize the disease precisely with a 5-year project involving 40 subjects with JP. During the study, patients will be placed on a program of preventive cleanings and checkups similar to the program established at the DCRC for average patients. "Our JP subjects have all had surgical treatment for periodontitis and are much more susceptible to disease than are average patients," he says. "Now that we have some experience with selective cleaning schedules for average patients, we are more confident in dealing with JP subjects."

While battling the disease with dental hygiene, the researchers will evaluate tissue response to the therapy in these subjects. They will identify and measure the action of AA on gum, bone, and blood cells. Each patient will receive a complete medical and dental examination and will provide a family history to allow the researchers to test the hypothesis that an X-linked chromosomal defect impairs the immune system and makes the patient susceptible to JP.

"I believe we are on the verge of a breakthrough in being better able to diagnose, treat, and perhaps prevent this disease," Dr. Taichman says. "Our experiments on the mechanism of leukocyte interaction with AA may help to accelerate this objective and to generate data useful for investigating other diseases."

Before Dr. Taichman and his colleagues began studying juvenile periodontitis, AA was described in the medical literature as being associated with heart valve disorders. Recently the DCRC team helped physicians at a local hospital to identify this organism, which was found on the heart valves of two patients.

Dr. Taichman suggests that the bacterium enters the bloodstream after successfully attacking and destroying tissue in the mouth. "We believe that the two patients at the hospital may have had juvenile periodontitis," he says. "We couldn't confirm the diagnosis because we didn't see the children, and the physicians are not educated to recognize JP; but all the clinical signs of JP seemed to be present."

Just as the study of bacteria in the mouth may yield information useful in medicine, research into medical problems sometimes impacts on the dental community. A method called X-ray fluorescence radiography was applied by Dr. Irving Shapiro, professor of biochemistry, and Dr. Peter Bloch, associate professor of radiological physics, both at the University of Pennsylvania, to measure lead in the teeth of children suspected of being poisoned by paint chips.

"Then one day, Peter and I were discussing a newspaper article that described dentists as being high insurance risks because of their rate of suicide. The article also cited dentists as having a high divorce rate and being prone to depression," Dr. Shapiro says. "We wondered if dentists had problems caused by inhaling mercury vapors. We wondered, in fact, if dentists were another form of mad hatters—hat makers in the 1800's who went crazy because they absorbed mercury used to soften the felt in hats."

Despite the development of new composite materials for dental use, most fillings include an amalgam of silver and mercury. A busy dental office may consume 3 pounds of mercury each month, according to Dr. Shapiro. The standard practice of handling mercury in premixed capsules has reduced much of the danger, but spills and the resulting inhalation of mercury vapors still occur.

The biological effects of mercury are not known exactly, but the liquid metal has been implicated in senile dementia and amyotrophic lateral sclerosis. "So we decided to use the X-ray fluorescence technique to measure the amount of mercury in the wrists and brains of dentists," Dr. Shapiro says.

With minor modifications, the technique was ready for application to the new problem. "Dr. Shapiro and Dr. Bloch had the equipment, methods, and techniques but lacked access to the exposed patient population," says DCRC Director Dr. Ship. "In this project, the DCRC's role was to serve as a consultant in epidemiology and to recruit the participants."

The center recruited 300 dentists, aged 45 to 64, from Pennsylvania, Delaware, and New Jersey. It also collected demographic and health information. Mercury levels in each subject were assessed at the DCRC and examined in Dr. Shapiro's laboratory.

Of the dentists studied, 18 with the highest levels of mercury accumulation showed abnormal neurological reactions. These were attributed to previous medical conditions in only five of the dentists. Those with low levels of mercury showed no neurological abnormalities.

Several dentists had mild, subclinical cases of carpal tunnel syndrome, a neurological disorder causing numbness in the lower arm and hand. Individuals with the highest mercury levels showed the most psychological distress as well as visual and perceptual changes. The researchers concluded that use of mercury as a restorative material can result in long-term health risks to dentists; but they stopped short of saying that any subjects in the study were actually poisoned.

"We showed that some apparently normal dentists have neurological dysfunction due to mercury," Dr. Shapiro says. "Whether the mercury interferes with their personal or professional performance—their

DCRC *continued*

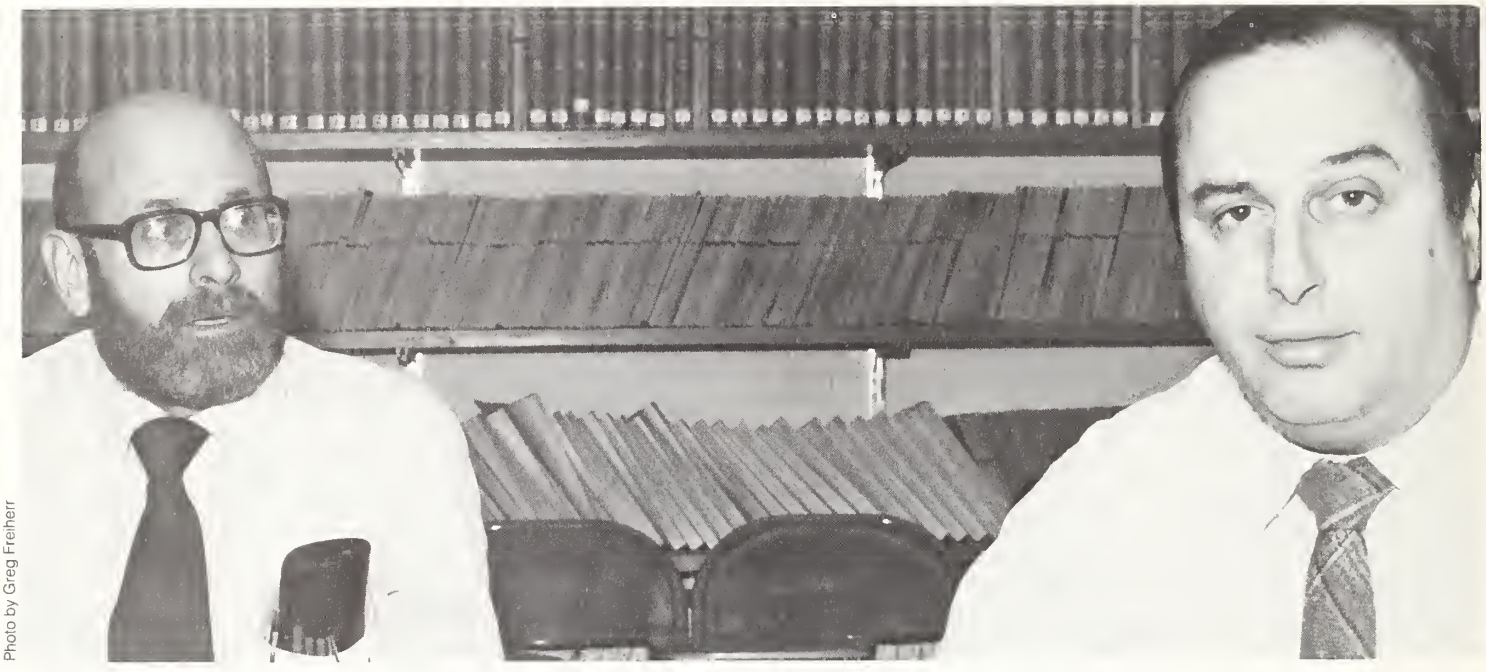

Photo by Greg Freiherr

Drs. Edward Korostoff (left) and Zeev Davidovitch of the University of Pennsylvania dental bioengineering center: *electricity to aid straightening of teeth.*

ability to repair holes in teeth and interact well with patients, friends, and relatives—is very difficult to evaluate. Our project was set up to examine a suspected relationship between mercury exposure and various aspects of neurophysiological function."

The risks of mercury exposure can be reduced by modifying the dental office, the researchers say. Tests for mercury in 54 offices revealed that the vapor level of the liquid increases sharply when linoleum floor covering is scuffed or carpeting is present in the area where restorative materials are prepared. Scuff marks and carpeting provide reservoirs in which spilled amalgam powder can reside. Controlled testing of these reservoirs by the DCRC researchers showed that mercury vapor levels increased 18 times above the ambient level when scuff marks were present and 28 times above the ambient level when floors were carpeted. Anyone exposed to mercury vapors from these reservoirs could be affected, which is why Drs. Shapiro and Bloch are now applying the X-ray fluorescence technique and a battery of neurophysiological tests in a followup study of the dental auxiliaries who prepare restorative materials.

Just as experience gained from medical studies was applied directly to the mercury study, so the use of electricity to speed the healing of fractures was applied to straightening teeth. At the University of Pennsylvania dental bioengineering center, Dr. Zeev Davidovitch, professor of orthodontics, and Dr. Edward Korostoff, professor of restorative dentistry, are collaborating in the design of a dental appliance that selectively administers electricity to teeth that are being mechanically moved. Dr. Davidovitch states that the electrical appliance is not designed to replace mechanical orthodontics. "The goal is simply to reduce the time needed for orthodontic treatment," he says.

The appliance consists of several batteries, a transistor, a resistor, a stainless steel cathode, and a gold-wire anode. Each component is embedded in acrylic. Only the tips of the electrodes are exposed. The anode and cathode are positioned on opposite sides of the tooth. Electricity flowing between the electrodes causes bone to form on one side of the tooth and to be resorbed on the other. According to the researchers, this formation and resorption of bone is mediated by changes in the normal levels of cyclic adenosine monophosphate (AMP) and cyclic guanosine monophosphate (GMP), two compounds present in periodontal ligaments and alveolar bone cells. Changes in AMP and GMP levels occur when wire and springs move teeth, the researchers say. Electrical stimulation accentuates the changes and thereby increases the rate of tooth movement, they believe.

Tests conducted for 7 to 14 days on female cats resulted in a 100 percent increase in the rate of tooth movement—an actual movement of 1 mm with the addition of electricity compared to 0.5 mm with only conventional braces. "The experiments were short-term because the cat is not exactly enthused about wearing this appliance," Dr. Korostoff says. "It is designed primarily for the human mouth and is, therefore, too large for the cat. Another problem is that the cat cannot bite properly and if the appliance is left in for very long, eating is disrupted, and poor nutrition could affect the response to electrical stimulation."

The researchers have now begun applying the technique clinically. They will install appliances in 30 subjects grouped according to age. Conventional orthodontic procedures will be modified with the placement of electrodes on one of the two canine teeth in

Photo by Greg Freiherr

Dr. Irwin Ship, director of the DCRC: *"Hopefully, collaboration between researchers in dentistry and medicine will better inform practitioners in both disciplines on how cooperation and shared knowledge can benefit their patients."*

each subject, allowing researchers to determine the rate of movement with and without electrical stimulation in the same patient. Thirty patients, similarly grouped, will serve as controls, receiving no electrical stimulation.

Starting 2 weeks after tooth extraction, electricity will be applied in the study group for 8 hours per day for 12 weeks. The entire course of treatment will continue for the usual 2 to 3 years. Tooth movement will be evaluated during and immediately following electrical stimulation and periodically thereafter.

The chance of tissue damage resulting from the application of electricity is all but discounted by the researchers. "Unlike drugs, which affect the entire body, direct electrical current has only a local effect, and we have seen no adverse local reactions in animal tissues," Dr. Davidovitch says. Careful examinations of the gums will be conducted regularly, however, to ensure that adverse effects do not occur.

Design of the appliance and methods for the study were drawn from the experience of orthopedic researchers at the University of Pennsylvania who have applied electricity extensively as an aid in the healing of fractures. "Coordinated efforts by medical and dental specialists are required," says Dr. Cohen, "if dental research is to achieve its full potential."

According to Dr. Ship, research at the center exemplifies what can be achieved when the dental and medical disciplines work together. "Hopefully," he says, "collaboration between researchers in dentistry and medicine will better inform practitioners in both disciplines on how cooperation and shared knowledge can benefit their patients." R

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Research into the repopulation rates of bacteria affecting oral tissue is funded by the National Institute of Dental Research. Study of juvenile periodontitis is supported by the National Institute of Dental Research. The study of mercury toxicity in dental personnel was funded by the National Institute for Occupational Safety and Health and the American Fund for Dental Health. Application of electricity to the movement of teeth is supported by Venture Technology, Inc. The University of Pennsylvania Dental Clinical Research Center is supported by the General Clinical Research Centers Program of the NIH Division of Research Resources.

Research Focus

Peritoneal Drug Delivery for Special Diabetics

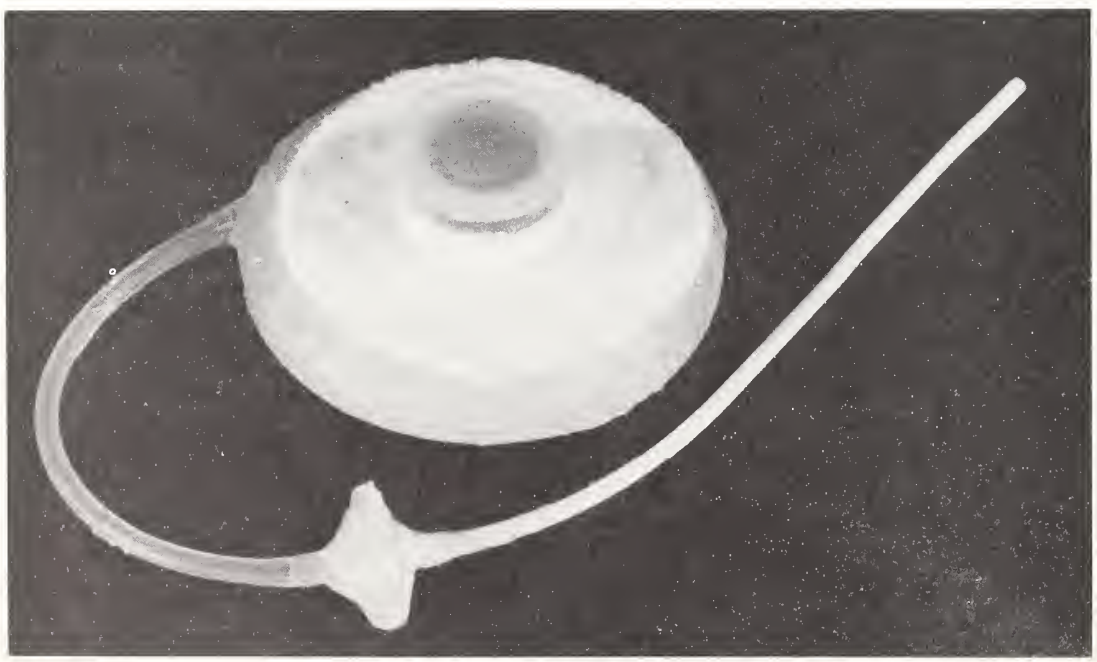
A new system for delivering insulin directly into the peritoneal cavity has eliminated recurrent and sometimes life-threatening infections caused by administering the drug through intravenous catheters, an unusual route of administration reserved for diabetics who do not respond to conventional injections of the drug.

"Subcutaneous tissue in these patients suddenly and without any apparent reason begins to degrade and inactivate insulin. Intravenous catheters may then be implanted," says Dr. R. Philip Eaton, professor of medicine at the University of New Mexico (UNM) in Albuquerque, "but after several weeks or even days, the catheters sometimes become infected or thrombose and obstruct the flow of blood."

To solve the problem Drs. Eaton and David Schade, associate professor of medicine at UNM, developed a system that delivers insulin directly to the peritoneum, where the portal vein absorbs and carries the drug to its target organ, the liver. The system, which has been approved by the UNM Institutional Review Board and is implanted under Food and Drug Administration guidelines, consists of a dacron and silicon port implanted near the umbilicus and sealed by the body's own skin. Insulin is injected through the port and into a tube that leads to the peritoneum. The system does not intrude into the circulatory system, it is completely sealed from external bacteria, and the insulin is self-sterilizing; for these reasons, the risk of thrombosis is eliminated, and the chance of infection is greatly reduced.

Since December 1981 the new system has been implanted in six patients whose recent medical history showed frequent and life-threatening infections or thromboses due to the use of intravenous (IV) catheters. Prior to implant, the patients averaged 14 days per month in the hospital. None was able to attend work or school. "They were in desperate situations," Dr. Eaton says. "One patient, over a 2-year period, had a total of 27 IV catheters implanted and then removed because of complications."

The peritoneal delivery system is still functioning well in five of the six patients, allowing each to resume normal activities free from the high risk of complications. The first system implanted was removed by attending physicians in Minnesota because of a suspected infection surrounding the injection port. "We think that multiple injections into the port, which in this patient was located below the skin, caused local pain and irritation," Dr. Eaton says. "Because of that problem we changed the port's location from an internal to an external site."



Peritoneal insulin delivery system: *buying time for the diabetic who doesn't respond to conventional injections of insulin.*

Self-injection of insulin into the peritoneal delivery system: *painless access to the target organ, the liver.*

The injection port is circular and about one-half inch in diameter. Its dacron cuff is sewn to the skin surface. The healing process causes skin to grow into the cuff and bond with it. "So now the patient injects directly into the port and not through the skin," Dr. Schade says. "Therefore we think infection is very unlikely. We've since implanted this modified system in three patients, and they're all doing well." The original system is also operating well in two of the first three patients.

The system was developed for a very specific purpose—to treat patients whose subcutaneous tissue degrades and inactivates insulin. The syndrome may appear at any stage in a diabetic's life, and it may disappear just as suddenly. "The syndrome is very poorly understood. It's a phenomenon that does not appear to be permanent," Dr. Eaton says. Generally it lasts for only a few months. Those receiving the drug delivery system at UNM, however, are exceptions. All have had the problem for at least 2 years and show no signs that it will end soon.

Time is one factor in deciding whether to implant the system; another factor is how seriously the disorder affects the diabetic. A candidate referred by an Oklahoma physician has been affected for 1½ years and has been in the hospital for the past 3 months.

"If I knew that within a few weeks this patient would respond to insulin shots, I would not consider implanting the system. But I don't know that, and there's no way to find out," Dr. Eaton says. "When we implant the system, what we're really doing is buying time, alleviating life-threatening situations that occur with intravenous treatment, and freeing patients from recurrent and sometimes lengthy hospital stays that prevent them from pursuing a normal social or economic livelihood."

This was the case for the most recent implant patient—an 8-year-old girl from Washington State who had experienced repeated life-threatening infections from IV catheters. About a dozen other patients, referred by physicians across the United States, are now waiting to receive the system.

Patients travel to the UNM General Clinical Research Center (GCRC) in Albuquerque for surgery that requires less than 45 minutes to complete. The technique, which was developed by former UNM surgeon Dr. Jay Gregory, requires only local anesthesia. Dr. William Sterling of the UNM surgery department now performs the operation. Dr. Sterling first inserts one end of a coiled silicon rubber tube into the peritoneal cavity, where it floats freely. The other end is attached to an injection port machined from polypropylene and fitted with a trilayer silicon rubber septum. He then sews the port into the skin so that the rubber septum protrudes through an incision near the umbilicus. Over a period of several days, skin grows into the dacron cuff that encircles the septum, forming a natural seal against infection.

The patient remains at the GCRC for about 2 weeks to ensure that the incision heals properly and that the device is correctly positioned and functioning. That period of time is also needed to train the patient to use the system. Usually the patient's physician visits the GCRC a few days after surgery to see how the system is implanted and how it works.

From the patient's viewpoint, there is little difference in administering insulin by subcutaneous injection or through the peritoneal device. "Diabetics have been self-injecting insulin ever since the treatment was available. The major difference between conventional treatment and peritoneal delivery is that the insulin is carried directly to the liver. Previously it could only be given subcutaneously, where it was absorbed by the veins and routed through the heart, through the arteries, and finally to the liver. By then most of the insulin was broken down."

The patient must be alert for signs of infection, but infection is not a serious concern. By providing a natural seal for the system, the risk of bacteria infecting the peritoneal cavity is minimal. Even insulin contaminated by bacteria poses little danger. "Prepared according to the U.S. Pharmacopeia formulation, the insulin contains antibacterial agents, so that bacteria contaminating the insulin will die within 24 hours," Dr. Eaton says. "The key to allowing these ingredients to work is to have a reservoir and a long tube, so that the insulin injected today doesn't reach the body until at least 24 hours later. The reservoir and tube we use hold the insulin for twice the required time."

Absorption by the portal vein of old insulin pushed into the peritoneal cavity by new injections is metered by the clinical formulation of the drug itself. The type of insulin recommended by the UNM researchers is formulated to be absorbed within 6 hours.

Dr. Eaton recommends that diabetics self-inject an appropriate amount of insulin into the peritoneal system periodically and especially at meals and before sleep, when they need a large supply of insulin. This schedule simulates the normal pattern of insulin secretion by the pancreas. It also manually approximates the action of insulin pumps, which are being developed by various research groups around the world. (See *Research Resources Reporter,* May 1979.) These pumps administer a continuous and varying flow of insulin tailored to the activities of the individual.

Five years ago, when Dr. Eaton and his colleagues began work on an implantable insulin pump at the Albuquerque GCRC, peritoneal delivery of insulin was only a concept, unproved and untried. Basic research by the two physicians determined that insulin injected into the peritoneal cavity is absorbed significantly, though not totally, by the portal vein, which transports it directly to the liver, as with insulin secreted by the pancreas.

"Almost in parallel with the scientific evolution of the concept for peritoneal delivery of insulin and the development of a pump, we found this unforeseen way of manually

administering insulin with the peritoneal port," Dr. Eaton says. "It's an ideal example of how the GCRC program is having a very real impact on patient care."

Meanwhile, the semiautomatic implantable pump developed at UNM has been used successfully in several patients. The pump can be programmed to release more or less insulin depending on daily schedules. It releases this insulin in a constant flow, which Drs. Eaton and Schade believe is better for the patient than sudden subcutaneous injections. The pump system also includes a memory of doses given each day.

"The advantage that the manual peritoneal system and the pump system have over conventional treatment is the route of administration—to the liver through the peritoneal cavity," Dr. Schade says. "The advantage unique to the pump is that it essentially runs itself, requiring only instructions on what to do. The pump is much more sophisticated than the manual system."

Although the manual system was developed primarily to circumvent a specific problem that is usually transient, even patients who eventually outgrow the syndrome may decide to continue using the peritoneal port system, which guarantees direct and painless administration of the insulin. "Having direct access to the liver *could* have tremendous long-term impact on the control of diabetes and its complications," he says, adding cautiously that the benefits will take years to document. "This is the problem with new therapies for chronic diseases. The data are years away. That's why we turned our attention first to patients who really need an alternative therapy. Patients who can gain definite benefits immediately." R

Additional reading:

Schade, D. S., Eaton, R. P., Warhol, R. M., Gregory, J. A., and Doberneck, R. C., Subcutaneous peritoneal access device for type I diabetic patients nonresponsive to subcutaneous insulin. *Diabetes* 31:470–473, 1982.

Development and testing of the peritoneal port for insulin delivery was supported by the American Diabetes Association, the General Clinical Research Centers (GCRC) Program of the NIH Division of Research Resources, the Juvenile Diabetes Foundation, and the Kroc Foundation. The UNM General Clinical Research Center is funded by the GCRC Program.

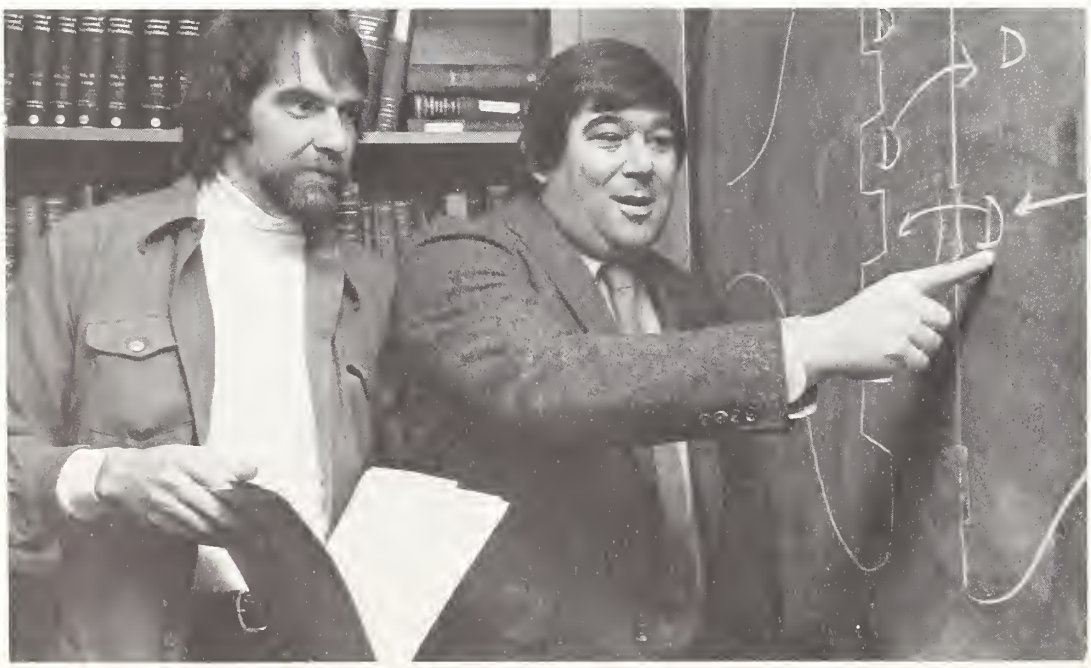
Hyperactivity Problems Identified in Adults

Stimulants may reduce or eliminate a variety of personality problems associated with adult hyperactivity, according to researchers at the University of Utah in Salt Lake City. "About two-thirds of our patients benefited from stimulant medication," says Dr. David Wood, a psychiatrist at the University of Utah.

Since the 1930's stimulants have been prescribed to treat children with hyperactivity, but little is known about the efficacy of stimulants in adults with the disorder. The need for such research is reflected by the severity of the problem. According to researchers at the University of Utah General Clinical Research Center (GCRC), approximately two-thirds of all hyperactive children may continue to have psychological problems as adults. These patients may be misdiagnosed as having anxiety, mood disorders, or simply being prone to antisocial behavior.

In 7 years of studying adult hyperactivity, Dr. Wood and other researchers at the Utah GCRC have tested about 200 patients. A major focus has been to evaluate the ability of stimulants to relieve symptoms of adult hyperactivity, which include motor hyperactivity, attention deficits, moodiness, and explosive temper.

The Utah researchers tested the stimulant pemoline in a 6-week trial involving 64 hyperactive adults. The re-



Drs. Frederick Reimherr (left) and David Wood, hyperactivity researchers at the University of Utah: *two-thirds of all hyperactive children may continue to have psychological problems as adults.*

searchers found that patients who were extremely hyperactive as children responded significantly better to pemoline than did other patients. Dr. Frederick Reimherr, a member of the Utah research team, says that patients who were not overly hyperactive as children often developed drug side effects including headache, nausea, cramps, anorexia, and insomnia. Four patients discontinued the drug therapy because they could not tolerate these effects.

Some patients responded immediately. Others responded only after side effects became tolerable and the dosage was increased. Some responded favorably only after receiving twice as much of the drug as other patients.

"Patients who responded well reported that, after treatment, concentration became easier, their attention wandered less, and they were able to complete tasks," says Dr. Paul Wender of the Utah team. "There was a decrease in motor activity and talkativeness. Thinking was slowed. These individuals found themselves listening to their spouses for the first time. Outbursts of temper were less severe and less common. Subjects reported that they felt less burdened and that they were able to endure everyday stresses and strains."

The effects seemed different from those reported by normal people who abuse amphetamines and experience exhilaration, loquaciousness, excitement, and restlessness. "The improvement was similar to that seen in children with hyperactivity who show a good drug response," says Dr. Wender. "Although one man rated his response as slightly improved, his wife was extremely enthusiastic about this improvement and said that years of marital difficulties had been arrested; she was no longer considering divorce."

This recent study of pemoline was developed from a trial led by Dr. Wood in 1975, in which the effects of the euphoric stimulant methylphenidate hydrochloride and the stimulant pemoline were compared. Fifteen subjects in that study were given methylphenidate. Two weeks later 11 subjects were switched to pemoline or tricyclic antidepressants. If the patient responded well to pemoline, it was continued. If he or she responded well to methylphenidate but failed to react to pemoline, the patient was put back on methylphenidate. Those who did not respond favorably to either drug were then given antidepressants. At the end of the study, which lasted 12 months, 8 of the 11 subjects were judged by the researchers as having an overall good response to drug treatment. Some patients responded to more than one drug. Fifty-three percent of the patients responded favorably to methylphenidate, 33 percent improved with pemoline, and 8 percent transiently improved when receiving tricyclic antidepressants. The rest did not respond to any drugs.

"Those responding to the drugs exhibited an increase in concentration, energy, and calmness and a decrease in irritability and moodiness. But none of the patients reported an increase in 'happiness' after methylphenidate treatment," says Dr. Wood. The researchers found that behavior improvement of patients could be maintained for months on low dosages of methylphenidate.

Such a failure to develop tolerance is characteristic of the response of hyperactive children, unlike that in stimulant abusers, who must rapidly increase dosage to obtain the desired effects. Patients who responded to pemoline treatment improved markedly more than those who responded to methylphenidate. "These patients became less anxious, less irritable, and less angry," he says. "Moods became stable and the subjects became less impulsive."

The researchers believe that patients who responded to stimulants may be hyperactive due to a persistent biological abnormality. Dr. Wender says that research by other investigators showed a higher incidence of alcoholism and personality defects among parents whose natural children were hyperactive than among parents who had adopted hyperactive children.

Accounts given by patients studied by the Utah researchers indicate that approximately one-third of their parents and one-fifth of their siblings were alcoholics or abused other drugs. Of the patients' 34 children, 41 percent had been independently diagnosed by other psychiatrists as being hyperactive. These observations indicate that hyperactivity may be inherited and that in some instances hyperactivity is a childhood forerunner of difficulties in adult life, says Dr. Wender.

Other evidence supporting the theory that some types of the hyperactive syndrome are hereditary stems from research into the effects of stimulants. Because stimulants act on the metabolism of nerve cells in the brain, Dr. Wender says, hyperactive individuals who respond to these drugs may do so because the drugs correct defects involving certain neurochemical messengers. This may explain why some hyperactive children outgrow the disorder: their neurotransmitter levels may naturally become normal, according to Dr. Wender.

He says there is an increasing amount of evidence suggesting that hyperactivity is associated with a deficiency of dopamine, a neurotransmitter that controls emotional response and complex movements. Stimulants are more effective than tricyclic antidepressants in controlling hyperactivity in children, he points out, and stimulants increase dopaminergic activity, while antidepressants increase noradrenergic and serotonergic neurotransmitter activity in the brain.

Drs. Wender, Wood, and Reimherr now are looking at cerebrospinal fluid for possible abnormalities that might reflect deranged brain metabolism. They have obtained cerebrospinal fluids and 24-hour urine samples from hyperactive adults to measure dopamine and other neurotransmitter levels. Dr. Wender says that preliminary results may indicate a deficiency in dopamine metabolism.

The researchers are conducting further tests that may determine the origin of hyperactivity. They also hope to find improved methods of drug treatment by testing several compounds that previously have not been used to treat hyperactivity. These new compounds include phenylalanine, a naturally occuring amino acid, and deprenyl, a monoamine oxidase inhibitor. ☈

Additional reading:

1. Wood, D., Reimherr, F., Wender, P., and Johnson, G., Diagnosis and treatment of minimal brain dysfunction in adults. *Archives of General Psychiatry* 33:1453–1460, 1976.
2. Wender, P., Minimal brain dysfunction: an overview. In *Psychopharmacology: A Generation of Progress* (Lipton, M. A., DiMascio, A., and Killman, K. F., eds.). New York, N.Y., Raven Press, 1978, pp. 1429–1434.
3. Wender, P., Reimherr, F., and Wood, D., Attention deficit disorder ("minimal brain dysfunction") in adults. *Archives of General Psychiatry* 38:449–456, 1981.

Research into hyperactivity at the Utah GCRC is supported by the General Clinical Research Centers Program of the NIH Division of Research Resources, the National Institute of Mental Health, and Abbott Laboratories.

Vitamin E May Prevent Development of Tumors in Mice

Vitamin E at controlled levels in the diet may inhibit the proliferation of tumorigenic cells, according to a recent research study with mice at the Boston University School of Medicine. Although previous research in mice has indicated that vitamin E can prevent carcinogen-induced mutation of a normal cell into a tumor cell, this study demonstrates that vitamin E can inhibit sarcoma cells from developing into tumors.

If similar results can be demonstrated in humans, then certain doses of vitamin E may prevent, not only initial tumor growth, according to researchers, but also the metastasis of cells from the original tumor. It is hoped that this might prevent the recurrence of tumors from the small number of tumor cells left following surgery for breast cancer or other solid-tumor cancers, according to Dr. Laurence Corwin, professor of microbiology at Boston University School of Medicine.

The purpose of Dr. Corwin's study with Dr. Michael Kurek, currently an applications specialist at the Millipore Corporation in Massachusetts, was to determine how vitamin E and dietary fat interact to affect tumor development. Several research studies have indicated that level of fat and type of fat appear to be important factors in tumor progression and that, with the exception of melanoma cells, most cancer cells grow best in animals fed diets high in polyunsaturated fats (PUFA's), which suppress the immune system.

The quantity of vitamin E needed to successfully prevent development of certain mouse sarcoma cells into tumors is dependent on the amount of PUFA's in the diet and on the number of cancer cells present, according to Dr. Corwin. He and Dr. Kurek demonstrated vitamin E protection against tumor production by varying the levels of dietary PUFA's and of vitamin E. They fed one group of mice 0.5 gram of vitamin E per kilogram of a diet high in PUFA's and a control group, a diet high in PUFA's but without the vitamin E supplement. They injected the mice with derivative sarcoma cells that they had previously demonstrated grew best in PUFA's. Mice fed the vitamin E supplement diet developed significantly fewer tumors than mice fed the unsupplemented diet. Similar results were produced with mice injected with sarcoma cells from the parent cell line, which the investigators had previously demonstrated grew best in saturated fats. Mice fed 0.5 gram of vitamin E per kilogram of a diet low in PUFA's developed significantly fewer tumors than mice fed an unsupplemented diet low in PUFA's.

"For vitamin E to be effective in preventing the growth and development of tumorigenic cells into tumors, dosage is important," says Dr. Corwin. "In one study we varied the vitamin E dosage in mice. We observed a bell-shaped response curve that indicated an optimum preventive dose of vitamin E that works, given a certain level and type of fat and number of tumor cells. We also found that if we gave the mice too much vitamin E, the vitamin lost its ability to protect against tumor development. Megadoses appear to decrease the tumor-preventing action of vitamin E. Our in vitro treatment of tumor cells with excessive levels of vitamin E corroborates this conclusion."

"It is difficult to extrapolate this data to humans by making dietary recommendations of vitamin E intake," adds Dr. Corwin. "I believe that vitamin E would work in humans, but I can't say what the proper dose would be. A preventive dose may very well correspond with the current recommended daily allowance of 12 to 15 international units. I say this because we recently found that vitamin E protects against tumor production in mice even at 0.05 gram per kilogram of diet, which is the normal vitamin E requirement in the diet of a mouse. Thus, popping vitamin E pills is certainly not what I'm recommending."

Dr. Laurence Corwin: *inhibiting the growth of mouse tumor cells with vitamin E.*

Vitamin E inhibits tumor production by strengthening the antigenicity of tumor cells, according to Dr. Corwin. Antigens are substances that evoke a specific immune response. Most tumor cells have weak antigens, which may not trigger the immune system, allowing them to develop into tumors. By strengthening the antigens of these cells, vitamin E exposes them to recognition and attack by the immune system. Increased antigenicity sparks a strong enough immune response to prevent the tumor cells from proliferating into tumors, according to Dr. Corwin.

"We demonstrated this in vitro," asserts Dr. Corwin. "We found that sarcoma cells grown in a medium containing vitamin E after a few generations provoked a much stronger immune response in vitro than sarcoma cells that had been cultivated in the same medium without vitamin E. Our research focus now is to identify what specific part of the immune system is responding to this increased antigenicity."

Additional reading:

1. Kurek, M. P., and Corwin, L. M., Vitamin E protection against tumor formation by transplanted murine sarcoma cells. *Nutrition and Cancer*. In press.
2. Corwin, L. M., Varshavsky-Rose, F., and Broitman, S. A., Effect of dietary fats on tumorigenicity of two sarcoma cell lines. *Cancer Research* 39:4350–4355, 1979.
3. Tengerdy, R. P., Heinzerling, R. H., and Nockels, C. F., Effect of vitamin E on the immune response of hypoxic and normal chickens. *Infection and Immunology* 5:987, 1972.
4. Stephenson, J. R., and Aaronson, S. A., Antigenic properties of murine sarcoma virus-transformed BALB/3T3 nonproducer cells. *The Journal of Experimental Medicine* 135:503–514, 1972.
5. Shamberger, R. J., Baughman, F. F., et al., Carcinogen-induced chromosomal breakage decreased by antioxidants. *Proceedings of the National Academy of Sciences* 80:1461–1463, 1973.

Research on vitamin E protection against tumorigenesis is supported by the National Cancer Institute, the U.S. Department of Agriculture, and the Biomedical Research Support Grant Program of the NIH Division of Research Resources.

Research Resources Reporter
November 1982

Information Exchange

Research Highlights

Abnormal DNA fragments have been identified in DNA/anti-DNA antibody immune complexes isolated from systemic lupus erythematosus (SLE) patients by researchers at Harvard Medical School in Boston, Massachusetts. The discovery may explain the origin of antibodies against the patient's own tissues in this disease.

Two classes of abnormal DNA were identified in the complexes isolated from serum and plasma of SLE patients. In both, the guanine-cytosine (G-C) content differed significantly from that in normal DNA. The small abnormal DNA fragment (mw 25,000) had an average G-C content equal to 55 percent of the total of bases, that is, the purine and pyrimidine content. In the large fragment (mw 100,000) the G-C content was 45 percent of the total of bases. Normal human DNA has a G-C content of 38 to 40 percent of the base total. "Such unusually high G-C content can alter DNA structure so that it may become a target for antinuclear antibody production," says Dr. Hiroshi Sano, principal investigator. He also points out that DNA with high levels of G-C sometimes forms unusual structures such as triple-stranded forms, left-hand DNA, and bent DNA. Presumably, these bizarre forms, significantly different from normal cellular DNA, could trigger the immune system to form anti-DNA antibodies.

Dr. Sano explains that the G-C-rich fragments in SLE could be produced in two different ways. First, chromosomal DNA could be degraded randomly into fragments, and some of these with high-level G-C content might stimulate the formation of antibodies. Secondly, chromosomal DNA might be prone to break at G-C-rich regions, resulting in release of a high concentration of G-C-rich fragments into the blood, which might induce antibody formation. DNA hybridization studies indicated that both DNA fragments isolated from the immune complexes originated from human nuclear DNA.

SLE is one of the autoimmune diseases in which the body manufactures antibodies against itself. Some of the symptoms of SLE have been postulated to result from immune complexes—antigen-antibody-complement—that are deposited in various tissues. Autoantibodies may also combine directly with the patient's tissues. White blood cells migrate to these areas and phagocytize the complexes, but in the process they spill enzymes that cause inflammation and tissue injury. Joints, skin, blood vessels, the nervous system, kidneys, and often other organs of the body become chronically inflamed and injured. The disease is not uncommon, and studies indicate that more than 95 percent of the patients have antinuclear antibodies.

The body's immune system normally recognizes its own tissues as "self" and does not attack them. If cellular constituents such as nucleoprotein become sufficiently altered, however, the immune system may react to destroy them, as it does to a foreign invader of the body. The cause of these tissue alterations in autoimmune disease is not known, although it has been postulated that in certain cases they may result from viral infection.

Recently Drs. Sano and Chikao Morimoto of Harvard Medical School, Boston, have isolated DNA fragments with high G-C content from lymphocytes of SLE patients. These fragments were somewhat larger than those isolated from the immune complexes, but the G-C content was approximately the same. The researchers believe that these fragments could also serve as antigens to induce formation of autoantibodies that could react to the patient's own tissues.

Technician readies DNA samples for electrophoresis: *looking for abnormal DNA fragments that may induce autoimmune response in patients with SLE.*

Additional reading:

1. Sano, H., and Morimoto, C., DNA isolated from DNA/anti-DNA antibody immune complexes in systemic lupus erythematosus is rich in guanine-cytosine content. *Journal of Immunology* 128: 1341–1345, 1982.
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3. Koffler, D., Agnello, V., Thoburn, R., Kunkel, H. G., Systemic lupus erythematosus: prototype of immune complex nephritis in man. *Journal of Experimental Medicine* 134:169, 1971.
4. Glass, D., and Schur, P. H., Autoimmunity and systemic lupus erythematosus. In *Autoimmunity* (Talal, N., ed.). New York, N.Y., Academic Press, 1977, p. 536.

Research into studies of abnormal DNA in systemic lupus erythematosus is supported in part by the Biomedical Research Support Grant Program of the NIH Division of Research Resources and by the Arthritis Foundation.

Research Service

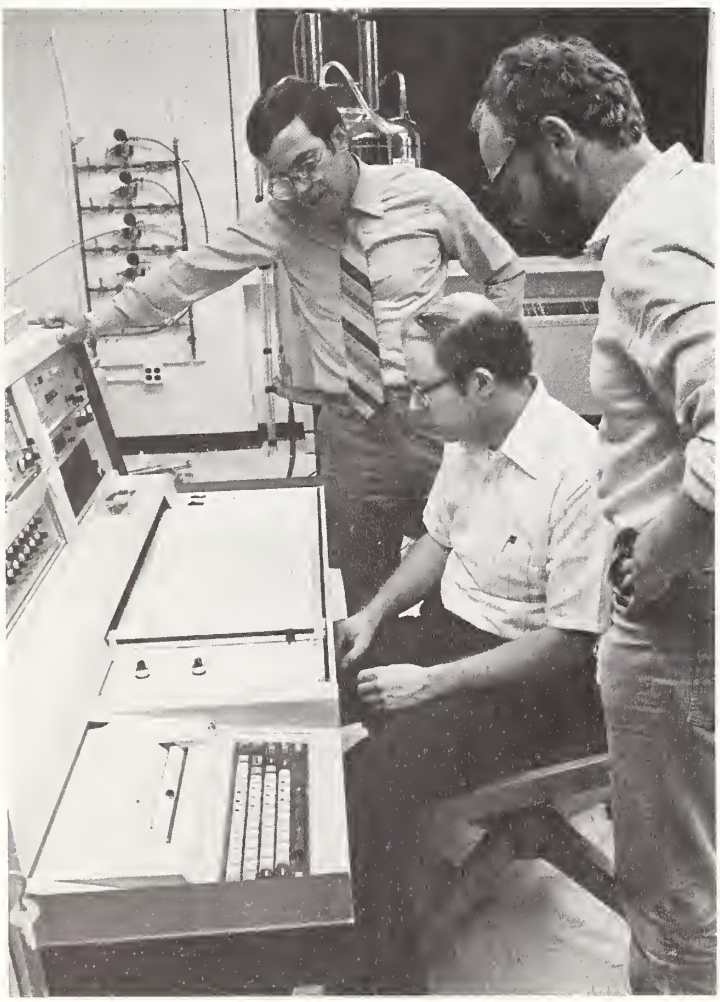
Multinuclei NMR Spectroscopy Resource

A resource that combines multinuclei nuclear magnetic resonance (NMR) spectroscopy with data processing capabilities is available at Syracuse University, New York. The resource is supported by the Biotechnology Resources Program of the NIH Division of Research Resources.

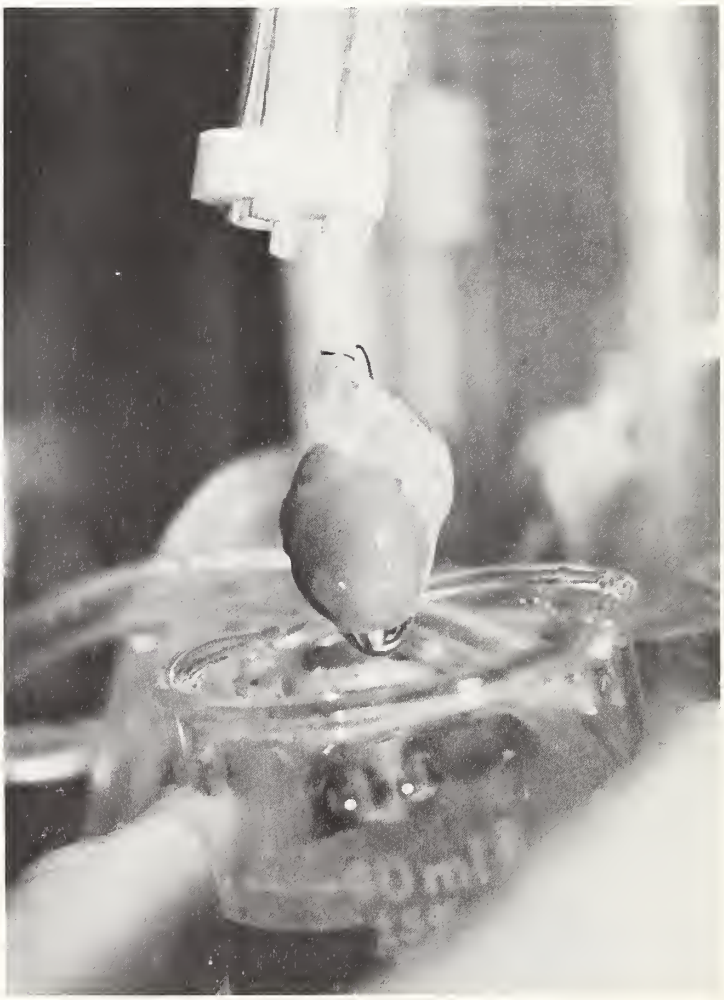
With NMR spectroscopy, scientists study the structure and interaction of molecules. When atoms are placed in a strong, uniform magnetic field and are exposed to a radio signal tuned to specific frequencies, the nuclei absorb and retransmit the radio signal. Resulting data indicate the sample's molecular structure. A multinuclei NMR spectrometer enables scientists to study molecules containing more than one type of atomic nucleus.

The Resource for Multi-Nuclei NMR and Data Processing is intended primarily for scientists whose studies require lengthy periods of data acquisition and highly sensitive NMR spectroscopy of ^{13}carbon, ^{15}nitrogen, and ^{31}phosphorus nuclei. Researchers can communicate directly with the Syracuse University resource computer by telephone. Through NMR/SPECNET, scientists can obtain data from experiments in progress or send raw data to the resource computer and receive real time, digital, or graphic output. The resource soon will sponsor semiannual workshops and training programs and will make available videotape instructions demonstrating the

Dr. George Levy (left), director of the Resource for Multi-Nuclei NMR and Data Processing with staff members Drs. Paul Marchetti and A. Ejchart (right): *providing data acquisition for lengthy NMR studies involving ^{13}carbon, ^{15}nitrogen, and ^{31}phosphorus.*



Rat heart studied at Syracuse University: *model for metabolic studies aimed at protecting the human heart during open heart surgery.*



NMR spectrometer's operation and the computer capabilities.

According to Dr. George C. Levy, director of the resource, the facility is the first in the country to combine NMR spectroscopy with spectroscopic data processing. The laboratory contains two high-field spectrometers and two computers. Primary instrumentation includes a Bruker WM–360 wide-bore 8.5 Telsa multinuclear NMR spectrometer. Broadband probes and solenoid coil probes enable the study of small to moderate-sized samples that are from less than 0.3 ml to 1.5 ml. Other resource instrumentation includes a 3.5 Telsa wide-bore multinuclei NMR spectrometer and a 5.8 Telsa narrow-bore multinuclei NMR spectrometer.

The data processing equipment includes a Data General MV–8000 32-bit minicomputer running a graphics-implemented spectral data reduction software system for one- and two-dimensional NMR spectroscopy. Two high-speed color graphics terminals are interfaced directly with the resource computer. These terminals are based on Lexidata 3400 image processors and have a direct memory access (DMA) interface to the 32-bit computer. Features of the spectral data processing system ORACLE, which is copyrighted, include full floating point computation and extended capabilities for quantification of spectral lines, cross-correlation spectroscopy, spin relaxation experiments, and general spectrum conditioning including sophisticated baseline correction algorithms. A multilayered architecture with automatic operations by default and several levels of manual overrides makes ORACLE both powerful and easy to use. Spooled output includes versatile formats of digital plots, which are fully annotated with text.

Graphics terminals and plotters in remote laboratories are supported through standard telephone connections. Scientists in remote laboratories can interact with resource personnel through the computer for the purpose of monitoring experiments in progress at the resource, thereby eliminating the need for travel to the resource. Full data sets can be transmitted to or received from remote laboratories, and interfaces to commercial spectrometer data formats are available.

The laboratory houses a biochemical preparations facility and office space for visiting scientists and coworkers. In addition, the two major software systems developed at the resource, ORACLE and ORACLE 2D, which is also copyrighted, are being disseminated to other laboratories.

For further information, contact:
Dr. George C. Levy, Director
Resource for Multi-Nuclei NMR and Data Processing
Department of Chemistry
Syracuse University
Syracuse, New York 13210

Meetings

November 14–17, 1982

Title: *3rd Annual Meeting of the Society of Environmental Toxicology and Chemistry*
Location: *Arlington, Virginia*
Contact: *Richard E. Tucker*
P.O. Box 352
Rockville, Maryland 20850
Telephone (301) 468-6704

November 16–18, 1982

Title: *20th Annual International Medical and Laboratory Instrumentation Congress and Exhibition*
Location: *Washington, D.C.*
Contact: *John L. Wolf*
AIMLI
11310 Palisades Court
Kensington, Maryland 20895
Telephone (301) 946-6464

November 29–December 1, 1982

Title: *Immune Networks*
Location: *New York , New York*
Contact: *Conference Department*
The New York Academy of Sciences
2 East 63rd Street
New York, New York 10021
Telephone (212) 838-0230

December 2–3, 1982

Title: *16th Annual Meeting of the American College of Chemosurgery*
Location: *New Orleans, Louisiana*
Contact: *Cheryl Nordstedt*
Convention Office
1567 Maple Avenue
Evanston, Illinois 60201
Telephone (312) 869-3954

December 2–4, 1982

Title: *2nd International Symposium on Medical Virology*
Location: *Anaheim, California*
Contact: *Luis M. de La Maza, M.D.*
Department of Pathology
University of California
Irvine Medical Center
101 City Drive
Orange, California 92668
Telephone (714) 634-6868

December 2–4, 1982

Title: *The Flexibility of Endoscopy: Update December 1982*
Location: *New Orleans, Louisiana*
Contact: *Dr. Myron Lewis*
Course Director
The American Society for Gastrointestinal Endoscopy
13 Elm Street
Manchester, Massachusetts 01944
Telephone (617) 927-8330

December 3–5, 1982

Title: *International Society and Federation of Cardiology*
Location: *Caracas, Venezuela*
Contact: *E. G. J. Olsen, M.D.*
Department of Histopathology
National Heart Hospital
Westmoreland Street
London W1M 8BA, England

December 4–7, 1982

Title: *24th Annual Meeting of the American Society of Hematology*
Location: *Washington, D.C.*
Contact: *Registration Supervisor*
Charles B. Slack, Inc.
6900 Grove Road
Thorofare, New Jersey 08086
Telephone (609) 848-1000

December 4–9, 1982

Title: *41st American Academy of Dermatology Annual Meeting*
Location: *New Orleans, Louisiana*
Contact: *Cheryl K. Nordstedt*
1567 Maple Avenue
Evanston, Illinois 60201
Telephone (312) 869-3954

December 11–12, 1982

Title: *12th Annual Clinical Dialysis and Transplant Forum*
Location: *Chicago, Illinois*
Contact: *D. Chianchiano*
National Kidney Foundation
2 Park Avenue
New York , New York 10016
Telephone (212) 889-2210

December 19, 1982–January 1, 1983

Title: *8th Annual Bicentennial Medical-Dental Seminar*
Location: *Vail, Colorado*
Contact: *F. B. Glenn, M.D.*
7741 Southwest 62nd Avenue
South Miami, Florida 33143
Telephone (305) 661-6208

January 10–12, 1983

Title: *3rd Annual Meeting of the American Society for Laser Medicine and Surgery*
Location: *New Orleans, Louisiana*
Contact: *E. H. Drake, M.D.*
425 Pine Ridge Boulevard
Suite 203
Wausau, Wisconsin
54401
Telephone (715) 845-9282

February 28–March 4, 1983

Title: *International Academy of Pathology, U.S.-Canadian Division*
Location: *Atlanta, Georgia*
Contact: *N. Kaufman, M.D.*
1003 Chafee Avenue
Augusta, Georgia 30904
Telephone (404) 724-2973

March 2–5, 1983

Title: *4th Annual Meeting of the Society of Behavioral Medicine*
Location: *Baltimore, Maryland*
Contact: *Thomas J. Coates, Ph.D.*
Society of Behavioral Medicine
P.O. Box 8530
University Station
Knoxville, Tennessee
37996
Telephone (615) 974-5164

March 14–16, 1983

Title: *5th Charles River International Symposium on Laboratory Animals, "Biomedical Research: Importance of Laboratory Animal Genetics, Health, and Environment"*
Location: *Heidelberg, Germany*
Contact: *Symposium Chairman*
Charles River Foundation
P.O. Box 430
Wilmington, Massachusetts
01887
Telephone (617) 658-6000

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